REMARKS

Claims 1, 3, 4 and 6-18 were examined.

Applicants respectfully request entrance of the claim amendments after final, because they cancel claims, were made in response to the Examiner's suggestions and/or place the claims in position for allowance. Additional searching due to these amendments will not be necessary, since the Examiner has already searched both alternative components of the composition of claim 1 as well as the combination of the components of claim 1 as evidenced by the Examiner's rejections under 35 USC §102 and §103. Therefore, the prior search conducted by the Examiner encompassed now amended claim 1. In addition, no other claims have been amended.

Claim 1 has been amended to require bioadhesive nanoemulsions rather than the option of either bioadhesive nanoemulsions or proteosomes. Furthermore as requested by the Examiner, the claim has been amended to clarify the language particularly related to the complexed or coupled relationship of the proteosomes and bioadhesive nanoemulsions or bioadhesive nanoemulsions with the antigen of (a). Support for the amendment to claim 1 is found, in the Specification, at least at: page 1, lines 6-10; page 7, line 26 to page 8, line 3; page 8 lines 17-25; page 9, lines 11-16; page 14, lines 23-25; page 37, lines 11-17; page 39, lines 6-21; page 40, lines 3-6, and 10-15; page 43, lines 15-23; and page 44, lines, 3-11. The amendments are made for business considerations and to better tailor the claims to encompass commercially contemplated embodiments of the invention at the present time, and they have not broadened the scope of the original claims.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Applicants wish to express their thanks for the indicated withdrawal of previously made objections and rejections. Reconsideration and withdrawal of the remaining rejections of record in light of the following is respectfully requested.

Claim Rejections under 35 USC §112, second paragraph

Claims 1, 3, 4, 6-12 and 16-18 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite and requiring clarification "because it is unclear how a peptide can be "complexed" with a composition generally, rather than to elements within it." The Examiner requested clarification because it is allegedly "unclear how the antigen is being complexed with the composition as a whole, rather than being complexed with the proteosome or mixed with the bioadhesive nanoemulsion, or complexed with a compound within the emulsion."

Applicants respectfully traverse, however, without acquiescence to the allegation of indefiniteness for the claims as originally presented and in the interest of expediency, claim 1 has been rewritten above to clarify the nature of the protein or peptide antigen complexing with a proteosome, bioadhesive nanoemulsion or both to produce the claimed immunogenic composition. The allegedly confusing language of (b) related to a composition comprising the proteosomes, bioadhesive nanoemulsions, or both has been deleted to avoid confusion between the proteosome/bioadhesive nanoemulsion composition and said immunogenic composition. The above clarification requested by the Examiner now renders the 35 USC §112, second paragraph rejection moot.

Support for the amended claim clarification can be found on page 8, lines 18-22 in the Specification which indicate "the vaccine composition is preferably formed by: (a) bonding the hydrophobic material to the protein or peptide to form a hydrophobic-hydrophilic compound; and (b) admixing the compound with the proteosomes, bioadhesive nanoemulsions, or both such that the antigen is complexed with the proteosomes or nanoemulsion."

We request withdrawal of this rejection in view of the claim amendment.

Claim Rejections under 35 USC §102(b)

Claims 1, 3, 4, 6, and 10-17 were rejected under 35 USC §102(b) as allegedly anticipated by Lowell *et al.*, *Science* 240(4853):800-02 (1988).

Applicants originally traversed the rejection by arguing (a) that the reference does not teach the inclusion of an "exogenous hydrophobic material in a composition with endogenous sequence as claimed," (b) that the reference fails to disclose or suggest the use of bioadhesive nanoemulsions, and (c) that the reference fails to "disclose or suggest the use of neutralizing antibodies."

The Examiner responded that with respect to (a) and (b), the claims are drawn to compositions comprising an antigen comprising a peptide having "(i) an endogenous hydrophobic sequence of between about 3 and about 50 non-polar or uncharged amino acids;

(ii) added to the protein or peptide, an exogenous hydrophobic material comprising a sequence of between about 3 and about 50 non-polar or uncharged amino acids or a C8-C18 fatty acyl group; or

(iii) both (i) and (ii), wherein the antigen is complexed to a proteosome, a bioadhesive nanoemulsion, or both.

The Examiner thus concluded that the claims did not allegedly require the presence of bioadhesive nanoemulsions in every embodiment. As stated above, without acquiescence to the allegation of anticipation, claim 1 has been amended to require the presence of bioadhesive nanoemulsions with or without proteosomes in every embodiment.

The Examiner further stated that the claim allegedly required the presence of both compositions so long as either the proteosome composition or the bioadhesive nanoemulsion composition was present. The claim as presently amended requires the presence of bioadhesive nanoemulsions and therefore does not allow for the alternative of proteosomes alone with the antigen of (a).

The Examiner finally concluded that the claim allegedly would be anticipated by a reference that teaches only one from each set of alternatives. According to the Examiner the Lowell *et al.* reference allegedly teaches the conjugation of a synthetic peptide antigen to an exogenous lauroyl, and the conjugation of this conjugate to a proteosome. And because the previous claims did not require both of either set of

alternatives to be present, the traversal was not found to be persuasive. As stated above claim 1 has been amended to require the presence of bioadhesive nanoemulsion material in every embodiment.

The Applicants maintain that the reference (Lowell *et al.*) fails to disclose or suggest the use of bioadhesive nanoemulsions and therefore the claims as amended which all require the presence of bioadhesive nanoemulsions cannot be anticipated by Lowell *et al.*

The Examiner further asserted that with respect to (c), the antibodies are not part of the claimed invention, but rather are an intended result of the composition's administration. Applicants continue to traverse the accuracy of the Examiner's statement, however in view of the amendments and comments above further arguments pertaining to (c) are merely superfluous.

Applicants respectfully traverse the instant rejection because Lowell *et al.* fail to disclose or suggest the use of bioadhesive nanoemulsions. In the absence of such a disclosure or suggestion, Lowell *et al.* cannot anticipate the claims. Applicants respectfully request withdrawal of the 35 USC §102(b) rejection in view of these remarks.

Claim Rejections under 35 USC §102(e)

Claims 1, 3, 4, 6, and 10-17 were rejected under 35 USC §102(e) as allegedly anticipated by Lowell *et al.*, U.S. Patent 5,726,292 (the '292 patent). Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse.

The claims as now amended require the presence of bioadhesive nanoemulsion material in every embodiment. The '292 patent requires a hydrophobic anchor or foot in conjunction with a proteosome, and possibly a submicron emulsion. It was not contemplated or claimed by the '292 inventors that a endogenous hydrophobic sequence and/or an exogenous hydrophobic sequence along with the bioadhesive nanoemulsion alone or a proteosome and bioadhesive nanoemulsion mixture would create the beneficial immunogenic composition of the present invention.

Therefore, Applicants respectfully traverse the instant rejection because like the Lowell *et al.* reference discussed above, the '292 patent also fails to disclose or suggest the use of bioadhesive nanoemulsions. In the absence of such a disclosure or suggestion, the '292 patent cannot anticipate the claims.

In response to the Examiner's likely assumption that sub-micron emulsions are the same as bioadhesive nanoemulsions, one must look at the patentably distinct inventions by Lowell *et al.* which cover sub-micron emulsions (US Patent 5,961,970) and bioadhesive nanoemulsions (US Patent 5,716,637). Lowell *et al.* received US Patent 5,961,970 entitled "Submicron Emulsions as Vaccine Adjuvants" on October 5, 1999. The abstract describes the invention of '970 as "A vaccine adjuvant composition of an oil-in-water submicron emulsion that has about 0.5 to about 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, about 0.05 to 5% of a nonionic surfactant, about 0.00001 to 1% of an immunogen, and an aqueous continuous phase." The same inventors of the '970 patent above also were issued US Patent 5,716,637 entitled "Solid Fat Nanoemulsions as Vaccine Delivery Vehicles", granted February 10, 1998. The '637 patent issued from US patent application number 08/553,350 which is expressly incorporated by reference at page 37, lines 14-17 as a method of preparing solid fat nanoemulsions of the present invention. The abstract of the '637 patent states: "the present invention provides pharmaceutical vaccine compositions that are nanoemulsions of particles having a lipid core which is in a solid or liquid crystalline phase at 25°C., and which is surrounded by at least one phospholipid bilayer for the parenteral, oral, intranasal, rectal, vaginal or topical delivery of both hydrophilic and lipophilic immunogens." The '637 application further illustrates the differences between sub-micron emulsions and the bioadhesive nanoemulsions in the following text at Column 3, lines 8-20 and the accompanying figures 1A, 1B, and 1C:

> The new entity is a particulate vehicle which is denoted herein as a solid fat nanoemulsion or "emulsome." These compositions have features which are intermediate between liposomes and oil-in-water emulsions. Emulsome particles contain a hydrophobic core, as in standard oil-in-

water emulsions, but surrounded and stabilized by one or more bilayers or envelopes of phospholipid molecules, as in liposomes (FIGS. 1A, 1B and 1C). A key feature of these particles is that the core is composed of a lipid which in bulk form is in a solid or liquid crystalline phase, rather than an oil in a fluid phase.

The advantages of the nanoemulsion used in the present invention are described at Column 3, lines 24-29 of the '637 patent: "Emulsomes, having the characteristics of both liposomes and emulsions, provide the advantages of high loading of hydrophobic bioactive compounds in the internal solid lipid core and the ability to encapsulate water-soluble antigens in the aqueous compartments of surrounding phospholipid layers."

Given that there are clear distinctions between oil-in-water/sub-micron emulsions presented in the art and the bioadhesive nanoemulsions of the present invention, and given the claimed composition requires bioadhesive nanoemulsions, the composition of the present invention differs structurally from the '292 composition and thus is not anticipated.

Applicants respectfully request withdrawal of the 35 USC §102(e) rejection in view of these remarks, and the arguments presented in the prior response.

Claim Rejections under 35 USC §103(a)

Claims 7 and 18 were rejected under 35 USC §103(a) as allegedly being obvious over Lowell *et al.*, U.S. Patent 5,726,292 (the '292 patent). Applicants have carefully reviewed the statement of the instant rejection and respectfully submit that no *prima facie* case of obviousness has been presented.

Claims 7 and 18 are claims that depend on the claims discussed above regarding the 35 USC §102(e) rejection over the '292 patent. As Examiner is fully aware, each dependent claim contains all of the limitations of the claim from which it depends. The arguments above are therefore incorporated herein to overcome the current rejection.

The fact that the '292 patent fails to disclose or suggest the use of bioadhesive nanoemulsions as claimed and given that the composition differs structurally from the '292 composition, establish that the '292 patent does not teach or suggest the claim elements of the current application.

Accordingly, no *prima facie* case of obviousness is present because the '292 patent reference does not suggest the claimed invention.

Applicants respectfully request withdrawal of the 35 USC §103(a) rejection in view of these remarks.

Claims 7 and 18 were rejected under 35 USC §103(a) as allegedly being obvious over the '292 patent as applied to claims 1, 3, 4, 6, and 10-17 above, and further in view of VanCott *et al.*, *J Immunol Methods* 183:103-17 (1995). Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse.

The VanCott *et al.* reference does not remedy the deficiencies of the '292 patent reference, which is discussed above. Although VanCott *et al.*, (described in the Specification, beginning on page 5 line 20 through page 6 line 12) provides an assessment of the oligomeric structure and antigenic properties of purified gp160 protein, VanCott *et al.*, does not disclose the significance of hydrophobic peptide portions of oligomeric gp160 nor its complexing with either proteosomes or bioadhesive nanoemulsions. Furthermore, there is no language in VanCott *et al.*, which suggests that the immunogenic properties of the purified gp160 protein are related in any way to the use of bioadhesive nanoemulsions. Therefore, VanCott *et al.*, did not contemplate the advantages of using bioadhesive nanoemulsions to enhance immunogenicity.

Applicants also respectfully point out that VanCott *et al.*, does not provide any particular information on a composition for inducing antibody formation. The title indicates only that gp160 is a potential immunogen and VanCott *et al.*, does not provide any motivation to use gp160, a viral antigen, in combination with any particular composition. Moreover, VanCott *et al.*, concludes: "It is hoped that the use of oligo-gp160, which more accurately mimics the oligomeric structure of viral gp120/gp41 as an

immunogen along with adjuvants which preserve protein structure may induce an immune response with enhanced increased HIV-1 cross-reactivity and neutralization capacity."

VanCott also teaches away from using the truncated version of gp160 disclosed herein. For example, at page 109, first column, lines 14-18, the binding to the V3 loop, considered critical in binding neutralizing mAbs (see lines 5-8 of the same section) is attributed to affinity differences rather than increased accessibility, and is, in fact, not discussed further. Thus, gp160 (451) would not be likely to elicit neutralizing antibodies.

Accordingly, no *prima facie* case of obviousness is present because the '292 patent reference in combination with the VanCott *et al.*, reference does not disclose or suggest all the elements of the claims.

Applicants respectfully request withdrawal of the 35 USC §103(a) rejection in view of these remarks.

Claims 1, 3, 4, 6, 7, 10, 11, 16-18 were rejected under 35 USC §103(a) as allegedly unpatentable over any of the '292 patent, Lowell *et al.*, or Lowell *et al.* in view of VanCott *et al.*, as applied above, and further in view of WO 95/11700 (the PCT reference). Applicants have carefully reviewed the statement of the instant rejection and respectfully traverse.

As previously argued individually for the Lowell *et al.*, '292 patent and VanCott *et al.*, references, all the claim elements are not met with any of these references alone or when combined. The PCT reference alone or in combination with the other references also does not remedy the deficiencies of these references for the following additional reasons.

The PCT reference is specifically concerned with oil-in-water submicron emulsions (SMEs) as a vaccine adjuvant and does not teach or suggest successful use of bioadhesive nanoemulsions to elicit neutralizing secretion antibodies as claimed. The patentably distinct differences between the bioadhesive nanoemulsions of the present invention and the sub-micron emulsions of the PCT reference were previously described. Based on the PCT reference, it would not be obvious to a skilled person to try and modify

a sub-micron emulsion into a bioadhesive nanoemulsion, and complex the modified or gp160 antigen in the hope of producing a immunogenic composition capable of inducing neutralizing secretion antibodies.

Applicants also maintain that the PCT reference does not suggest or teach the use of oligomeric gp160. Applicants respectfully request withdrawal of the 35 USC §103(a) rejection in view of these remarks.

Claim 9 was newly rejected under 35 USC §103(a) as allegedly unpatentable over Lowell *et al.* in view of VanCott *et al.*, as applied above, and further in view of Desai *et al.* (PNAS 83: 8380-84).

For the reasons provided above regarding Lowell *et al.*, the '292 patent and VanCott *et al.*, Applicants traverse the rejection of claim 9. Although Desai *et al.* may teach a gp160 protein, it does not provide the elements of the claimed invention that are missing from the other references. Therefore, we request withdrawal of this rejection.

Double Patenting Claim Rejections

Claims 1, 3, 4, 6, 7, 10-18 were rejected as allegedly being unpatentable over claims 1, 2, 5, 7, and 8 of the '292 patent for non-statutory obviousness-type double patenting.

Claims 1, 3, 4, 6, 7 and 10-18 were newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7 and 8 of the '292 patent further in view of VanCott *et al.*, and Desai *et al.* as applied above.

As stated above, the compositions of the '292 patent differ from those in the current application as amended and these differences have been described above for both the 35 USC §102(e) and §103(a) rejections over the same art.

Accordingly, no *prima facie* case of obviousness-type double-patenting is present because the present invention is patentably distinct from the '292 patent reference in that '292 does not render obvious the elements of the claims.

Applicants respectfully request withdrawal of the double patenting rejections in view of these remarks.

Conclusion

In light of the above amendments and arguments, Applicants respectfully submit that claims 1, 3, 4, and 6-18 are in condition for allowance and respectfully urge early indication to this effect.

If the Examiner believes a telephone conference would expedite prosecution of this application, he is encouraged to telephone the undersigned at the number provided below.

Respectfully submitted,

Karen Babiyak Dow

Karen B. Dow
Reg. No. 29,684

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (858) 350-6108
Fax: (650) 326-2422

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